Author’s response to reviews

Title: Impact of antiviral treatment and hospital admission delay on risk of death associated with 2009 A/H1N1 pandemic influenza in Mexico

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Version: 3 Date: 12 March 2012

Author’s response to reviews: see over
To the attention of Dr. Diana Marshall
Editor-in-Chief, BMC Infectious Diseases

Submission of a revised research article

Tempe, March 09, 2012

Dear Dr. Diana Marshall

Please find enclosed a revised manuscript, “Impact of antiviral treatment and hospital admission delay on severity of 2009 A/H1N1 pandemic influenza in Mexico, April-December 2009”, by Gerardo Chowell, Cécile Viboud, Lone Simonsen, Mark A. Miller, Margot González-León, Santiago Echevarría-Zuno, and Víctor H. Borja Aburto, which we wish to resubmit for publication in BMC Infectious Diseases as a research article.

We have addressed all of the Reviewer comments in our revised manuscript. We have enclosed point-by-point responses to the Reviewer comments.

Our manuscript is not currently under consideration elsewhere. All authors have contributed to, seen, and approved the final, submitted version of the manuscript.

Yours sincerely,

Gerardo Chowell, Cécile Viboud, Lone Simonsen, Mark A. Miller, Margot González-León, Santiago Echevarría-Zuno, and Víctor H. Borja Aburto
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Reviewer's report
Title: Impact of antiviral treatment and hospital admission delay on severity of 2009 A/H1N1 pandemic influenza in Mexico, April-December 2009
Version: 2 Date: 13 February 2012
Reviewer: Mark I-Cheng Chen
Reviewer's report:
General comments
This manuscript addresses an important issue. Though an observational study with its inherent biases, it presents reasonable findings that may have relevance to public health and case management of influenza. The are specific issues where clarification and revisions are requested.

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Response:
Thank you for this comment. We are glad that the Reviewer finds our results relevant to public health.

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Major Compulsory Revisions
1. One key issue not raised in the methods was how the authors dealt with missing data. Certainly in such a large dataset based on routine medical notes, there would be missing data on details like onset dates and antiviral use. Were these cases excluded? Or, in the case of antiviral use, was it just assumed not to be prescribed if it was not in the system (or there was no medical record of it)? And in the case of onset dates, it would be helpful to know what proportion were missing the onset dates if excluded, or if some data imputation method was used. Onset dates can be particularly tricky for individuals who end up in ICU and are unable to give good clinical history.

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Response:
Thank you for this comment. We have indicated that records with missing information were excluded from the analysis, as specified in methods section. Overall we excluded only 4.8% of records due to missing information. Indeed, only 0.2% of all records had missing date of symptoms onset, 4% of inpatient records lacked information on admission delay, and antiviral treatment was missing in 0.1% of records. We included one sentence commenting on missing data in the caveats section of the Discussion.

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Minor Essential Revisions
2. Line 80: "prospective epidemiological surveillance system put in place especially for the 2009 influenza pandemic by the Mexican Institute for Social Security (IMSS)"
I think the word "especially" should be changed to "specifically).

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Response:
We agree with the Reviewer and have revised this sentence accordingly.

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3. Line 92: "ILI was defined as a combination of cough, headache, and fever (except for persons over 65 years)"
Then what about those over 65 years? Was a different case definition used? This needs to be clarified by a follow-up statement. Alternatively, drop this idea of ILI altogether (see below).

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Response:
Sorry, this was not clearly written. We have clarified the description of the case definition as follows: “ILI was defined as a combination of cough, headache, and fever and one or more of the following symptoms: sore throat, rhinorrhoea, arthralgias, myalgia, prostration, thoracic pain, abdominal pain, nasal congestion, diarrhea. For persons > 65 years presence of fever was not required and for infants, and irritability was added to the list of associated symptoms.” In our revised manuscript we have also provided a definition for patients who were admitted to the hospital with acute respiratory infection (ARI).

4. Line 121: “we stratified admission delay into two groups <=2 and >2” I think there should be a colon after the word groups.

Response:
We agree with the Reviewer and have revised this sentence accordingly.

5. Line 130-131: “The case fatality rate (CFR) measures the proportion of deaths from all symptomatic infections,” CFR is actually a ratio / proportion, not a rate. Suggest the authors consistently use the term “case fatality ratio” instead.

Response:
We agree with the Reviewer and have changed this term throughout the paper.

6. Line 133: “Here we estimated the case fatality rate among ILI cases (CFRili)” - denominator is all ILI?
The reviewer is uncertain if using ILI without confirmation adds much value. The denominator here includes non-influenza ILI, but it seems to me the the numerator (for CFRili) here is not ILI but deaths in confirmed cases who also had ILI. Or did the reviewer read this wrongly?

Response:
Sorry for this confusion. We defined CFRili as the proportion of ILI deaths among ILI cases. Hence both the numerator and denominator include non-influenza ILI, as ~2/3 of these cases and deaths have not received laboratory confirmation. We have clarified the definition of CFRili in the text.

If the intention is to capture some idea of the extent of ILI from pdmH1N1 influenza that was not tested, it must be noted that:
a) there’s a lot of influenza that is asymptomatic or does not fulfil the rather stringent criteria for ILI.
b) the numerator also misses deaths from influenza that were not tested (if they are referring to cases which were confirmed) or did not fulfil ILI criteria.
As a result, it is difficult to meaningfully compare CFRili with other quantities in the literature such as symptomatic CFR (which is somewhat similar to your CFRflu) or CFR estimates based on serology. Perhaps the authors could elaborate in the discussion on why they think CFRili was important, if they wish to retain it. One possibility is to use this for within Mexico comparisons (across states and waves), in which case the authors must provide satisfactory evidence that ILI data collection is consistent over time and geography, and emphasize that this is the key use of bringing up CFRili.
Response:
We agree with the Reviewer about the potential issues with dealing with ILI trends. As the reviewer points out, our goal here was to compare CFRili patterns across pandemic waves and geographic regions in Mexico. We have elaborated on the Reviewer’s point in the discussion and note that we did not find significant differences in ILI reporting between states (e.g., in smaller states).

7. Table 1: how are confirmed cases that say presented to outpatient and then subsequently hospitalised counted? Can the authors confirm that there is no double counting (e.g. that someone is counted in the hospitalized group even if already seen as outpatient?) The same applies to hospitalised cases that eventually die.

Response:
Our database contains one record for each individual based on the (de-identified) personal ID of each patient. The database includes information on the most up-to-date disease severity category for each patient (outpatient, inpatient, and death). One patient could have been seen in the outpatient setting, subsequently hospitalized, and then die. This patient would be counted as a death in our analysis. We can confirm that there is no double counting in our dataset. We added a sentence in methods.

8. Line 194-197: “Southeastern states had 2.6-3.3 fold higher rates of neuraminidase inhibitor administration compared to other regions (Table 3). This is consistent with most of the A/H1N1 burden in this geographic region occurring in summer 2009, when antiviral administration rates were highest (Figure 2B).” I’m not sure what the authors are referring to above. Since antiviral administration is measured as a proportion of confirmed cases diagnosed, why would the burden of disease (incidence) affect the proportion treated with antivirals? Unless the authors are actually referring to true antiviral treatment rate which is doses per population? The authors should clarify firstly what they mean here by “antiviral administration rates”, and if they are actually referring to proportions treated, then they should remove the line which correlates burden in the geographic region with the higher proportion treated.

Response:
Sorry the sentence was unclear. We just meant to say that higher antiviral use in Southeastern States could be explained by the fact that the Southeast experienced pandemic activity in summer 2009, at a time when antiviral use was widespread in the country due to concerns about the potential severity of the new virus. In contrast, other regions experienced major pandemic activity in fall 2009, at a time when antiviral use had declined (likely due to lesser concerns about severity). We have removed this section. We have also clarified throughout the manuscript that antiviral administration rates referred to the proportion of cases that were treated with neuraminidase inhibitors.

9. Line 246-7: “whereas for the group of A/H1N1 inpatients with admission delays >2days, antiviral treatment was not significantly associated with risk of death” The above is an important point. Suggest to rephrase to increase the emphasis, “whereas for the group of A/H1N1 inpatients with admission delays >2days, antiviral treatment did not significantly reduce the risk of death…”

Response:
We have revised as suggested by the reviewer.
Discretionary Revisions

10. Lines299-304, on the “southeastern region”
Their discussion on the above is a little disappointing. Was the southeastern region different in terms of socioeconomics? Or ethnic differences? Or urbanisation? A brief mention of such factors could strengthen the discussion.

Response:
This result is intriguing. We have elaborated a bit more on this finding in the discussion as suggested by the Reviewer. Specifically, We do not expect that socio-economic or ethnic differences played a role on this difference. We do not think socio-economic factors played a significant role given that all patients covered through the IMSS health system in Mexico are workers and their families.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests.
Reviewer’s report
Title: Impact of antiviral treatment and hospital admission delay on severity of 2009 A/H1N1 pandemic influenza in Mexico, April-December 2009
Version: 2 Date: 10 February 2012
Reviewer: Vernon Lee

Reviewer’s report:
This paper is an important contribution to the literature on the association between antiviral treatment and delays in treatment to severe outcomes. The sample size is appropriately large, covering multiple periods of the local epidemic, and across broad geographical areas. The authors have adequately addressed the main hypothesis, and the paper is well written. There are some issues that I hope the authors could clarify.

Response:
We are glad the Reviewer find our results are relevant and add to our understanding of the relation of admission delays and antiviral treatment on the risk of death in the inpatient setting.

1. It is interesting to note that the ILI definition is different from other classical definitions of ILI. While it is not an issue among those without PCR-confirmed influenza, is there any literature on the specificity and sensitivity of this definition for influenza.

Response:
We have clarified our definition of ILI as it was not clearly defined in the earlier version of the manuscript. See response #3 to reviewer #1.
We do not have additional information on the specificity and sensitivity of this definition for influenza; however some studies have explored related definitions (Gordon et al. 2010; Lucas et al. 2011).

2. How was the influenza testing done among the different groups of patients. Were more hospitalized and death cases tested, compared to those who only had ILI in the outpatient setting? Were more or less cases tested later in the course of the pandemic. It would be interesting to discuss this as if may have affected the results if anti-viral use was linked to testing.

Response:
We have documented elsewhere that testing rates for A/H1N1 influenza were stable at ~33% of all ILIs throughout the pandemic period and across geographic regions and age groups (Chowell et al. PLoS Med 2011). We have now included this information in the data description section.

3. It seems from the methods and results that severity was assessed broadly as outpatient, inpatient, and death. However, hospital admission itself was not an outcome variable unlike the case fatality rate. In which case, should the assessment of severity be more appropriately changed to assessment of mortality? And the title of the paper changed accordingly to impact on case fatality?

Response:
We have revised the title accordingly to reflect our focus on the risk of death.
4. The authors stratified the admission delay into two groups, but not antiviral treatment into those that receive treatment ≤2 and >2 days. Is there an implicit assumption that antiviral treatment is only given immediately upon admission to hospital. I would assume that antiviral treatment could be given before or some time after hospitalization. It would be important to explore the time to antiviral treatment and the relationship to the time to hospital admission, if this data was available.

Response:
This is a very good point. Our data on antiviral treatment only includes whether the patient received neuraminidase inhibitors during initial consultation or at admission (typically within 24hrs of admission). We have clarified this in the data description section. Unfortunately, data on the exact timing of the start of antiviral treatment were not available for our analysis. We have now indicated this as a caveat in the discussion.

5. Similarly, the reason for the antivirals administered more frequently to patients with short admission delay could be due to increased treatment in early-onset severity, rather than patients who may be well initially and therefore untreated, and deteriorated subsequently and needed hospital treatment. This possibility should be discussed in the absence of additional data to validate or refute this hypothesis.

Response:
We agree with the Reviewer. We have now discussed this issue in relation to our available data on antiviral treatment in the discussion.

6. Discussion, 1st paragraph, line 8. The analysis does not directly support the effectiveness of antivirals when administered during the early symptomatic phase (≤2 days). At best, this is an indirect extrapolation because the time to treatment data was not available.

Response:
We have revised this sentence appropriately as follows “Our findings suggest significant antiviral effectiveness when administered during the early symptomatic phase (≤2 days)...”

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I had received unrelated research grants from GSK in the past.